PLA 96-0958

CLINICAL REVIEW

PRODUCT: INTRON® A (INTERFERON ALFA-2b)

SPONSOR: SCHERING-PLOUGH, CORP.

INDICATION: FOR THE TREATMENT OF FOLLICULAR NON-HODGKIN'S LYMPHOMA

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SUBMITTED: AUGUST 7, 1996
APPROVED: NOVEMBER 6, 1997

Table of Contents

I. Introduction

The activity of interferon alfa (IFN-α) against Non-Hodgkin lymphoma (NHL) has been explored in a variety of clinical settings for nearly 20 years (1-12). Although IFN-α exhibited activity against transformed B-cells *in vitro* and has induced tumor regression in NHL as well as other malignancies, the exact role of IFN-α in the treatment of NHL has remained undefined. Interferons have been used as low- (3) or high-dose (4) monotherapy, in conjunction with conventional chemotherapy, and for maintenance of response post-chemotherapy (5, 6). The published results of a number of phase 1, 2 and 3 clinical trials, suggest that INTRON®A has activity in follicular lymphoma (FL). Based upon these data, Schering Plough audited one successful Phase 3 clinical trial conducted in France and Belgium by the Groupe d'Etude des Lymphomes Folliculaires (GELF study)[1] under the guidance of [redacted] these data were submitted in support of a Biologics Licensing Application (BLA) for the treatment of follicular lymphomas.

The GELF study compared the progression-free and overall survival in a subset of patients with poor prognosis follicular small cleaved cell (FSCC, IWF B) and follicular, mixed large and small cleaved cell (FM, IWF C) NHL, randomized to receive a multidrug, anthracycline-containing chemotherapy regimen with or without INTRON®A. The chemotherapy regimen, CHVP, utilized in this study consisted of cyclophosphamide, doxorubicin, teniposide (VM-26) and prednisone. This regimen differs from the CHOP regimen more commonly used in the United States in two ways. First, CHVP uses VM-26 in place of vincristine (Oncovin®) used in the CHOP regimen. Since VM-26 is more myelosuppressive, the dose of doxorubicin utilized is 50% less than the dose used in the standard CHOP regimen and the cycle duration is 25% longer for CHVP (28 days as compared to 21 days for CHOP). Secondly, the total duration of therapy and cumulative doses delivered are higher for CHVP since this regimen contains both a 6-month induction phase and a 12 month maintenance phase, for a total of 12 cycles delivered over 18 months, compared with a standard 6 months of CHOP therapy.

In addition to the data obtained in the audit of the GELF study, Schering-Plough has submitted a number of published literature references as supportive information. These include the results from several randomized, phase 3, observation-controlled studies evaluating the contribution of IFN-α 2a (ROFERON®A) or 2b (INTRON®A) for induction therapy in combination with cyclophosphamide (7) or chlorambucil (8). Results from an ECOG trial employing the COPA combination regimen with or without IFN (12) were also submitted. The final study included as supportive for this indication reported on patients receiving ROFERON®A maintenance *vs* observation following CVP induction (10, 11).

[1] A subgroup of the Groupe d'Etude des Lymphomes de l'Adulte (GELA).

II. Chronology for Product Licence Application

- August 8 1996: PLA #96-0598 is submitted to the FDA.
- August 25 1996: PLA #96-0598 filed.
- January 29 1997: Review of the submitted material is completed; non approvable letter issued.
- May 6 1997: Response to non approvable letter received.
- October 17 1997: Presentation to Biologic Response Modifier Advisory Committee.

III. Regulatory History

INTRON®A has been approved by the FDA for the treatment of a variety of neoplastic and viral diseases.

- January 1986: INTRON®A was approved for the first-line treatment of Hairy Cell Leukemia in patients 18 years of age or older. The recommended dosage is 2 million IU/m^2 administered intramuscularly or subcutaneously 3 times a week.
- June 1988: approved for the treatment of Condylomata Acuminata in selected adult patients with lesions of the genital and perianal region. The recommended dosage is 1 million IU intralesionally three times per week on alternate days, for three weeks.
- November 1988: approved for the treatment of patients with AIDS-related Kaposi's Sarcoma who are without systemic symptoms, who have limited lymphadenopathy and who have a relative intact immune system as indicated by CD4 count. The dosage recommended is 30 million IU/m^2 administered subcutaneously or intramuscularly 3 times a week.
- February 1991: approved for chronic hepatitis C at the recommended dosage or 3 million IU 3 times a week administered subcutaneously or intramuscularly.
- July 1992: approved for chronic hepatitis B at the recommended dosage of 30 to 35 million IU per week administered subcutaneously or intramuscularly.
- December 1995: approved for the treatment of malignant melanoma after surgical treatment of selected adult patients at high risk for systemic recurrence. The recommended INTRON®A treatment regimen includes induction treatment 5 consecutive days per week for 4 weeks as an intravenous infusion at the dose or 20 million IU/m^2, followed by maintenance treatment 3 times per week for 48 weeks as a subcutaneous injection, at a dose of 10 million IU/m^2.

IV. Proposed indication

INTRON®A interferon alfa 2b, recombinant for injection is indicated in conjunction with a doxorubicin-containing combination chemotherapy regimen for the treatment of patients 18 years of age or older with low to intermediate grade, high tumor burden, clinically aggressive follicular lymphoma.

V. Clinical Data

A. GELF Study

Clinical data were obtained from a randomized, multicenter, open label study in patients with follicular lymphoma conducted by the French cooperative Groupe d'Etude des Lymphomes Folliculaires (GELF). The trial stratified patients into two subgroups according to presence of low vs high tumor burden at study entry. Patients with low tumor burden were randomized to one of three arms: observation, oral prednimustine, or INTRON®A. Patients with high tumor burden were randomized to combination chemotherapy alone or chemotherapy plus INTRON®A. Patients with low tumor burden who demonstrated progressive disease on the low tumor burden portion of the study were eligible for registration and randomization (to chemotherapy or chemotherapy plus INTRON®A) in the high tumor burden study at the time of progression. The data submitted by the sponsor include only those patients with high tumor burden. A schema of the entire study is shown in Fig 1.

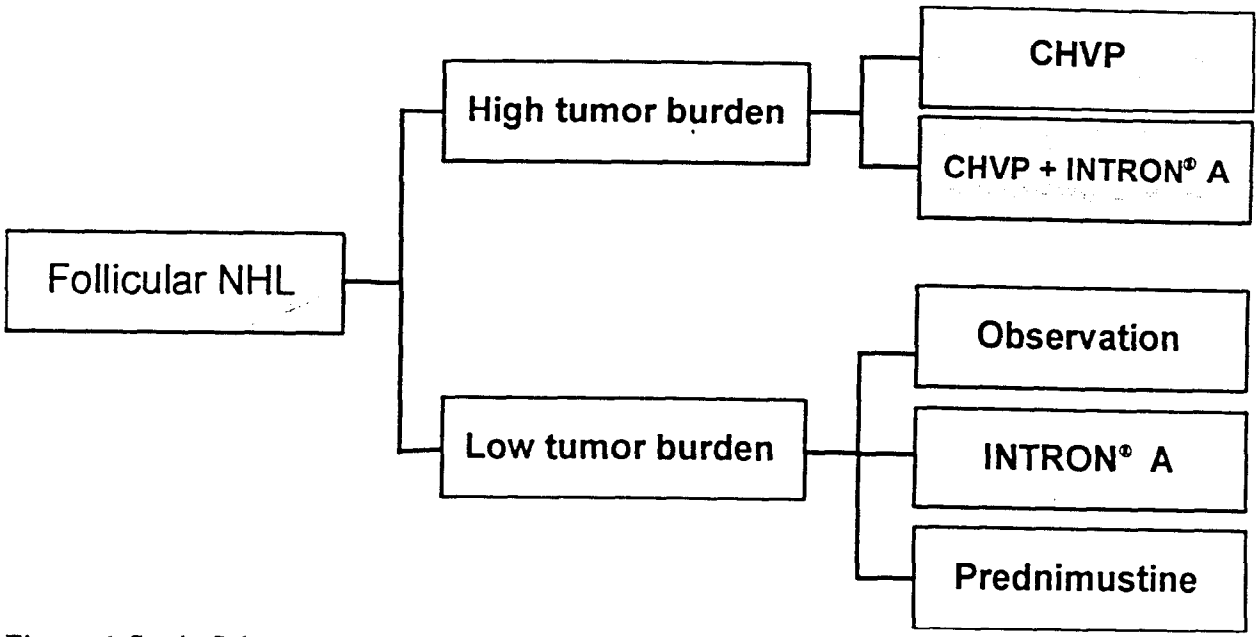

Figure 1 Study Schema
(The shaded area represents the part of the study pertinent to the indication being sought)

Study Design

Title Interferon alfa 2b recombinant (INTRON®A or SCH 30500) with combination chemotherapy for the treatment of patients with advanced, clinically aggressive follicular non-Hodgkin's lymphoma.

Objectives (per translated protocol)

1. To study the benefit of multiple-agent chemotherapy including an anthracycline administered during a prolonged period
2. To check if the effects of this multiple-agent chemotherapy are potentiated by a concomitant administration of low dose interferon-alfa

Efficacy Endpoints

1° Progression-free survival
2° Overall survival and objective clinical response rates

Safety Endpoints

1° Incidence of serious adverse events
2° Spectrum and severity of adverse events associated with the two treatment arms

Eligibility

- Histologically confirmed FSCC. (< 5% large non cleaved cells) or FM (5 to 50% large non cleaved cells) NHL [2], previously untreated (including no prior corticosteroid exposure)
- Age < 70 years
- "clinically aggressive" disease, defined as one or more of the following:
  - nodal or extranodal mass with a diameter > 7 cm
  - involvement of 3 sites each with a diameter > 3 cm
  - systemic "B" symptoms
  - splenomegaly..."extending to [the] umbilicus"
  - compression syndrome, ominous localization (e.g., tonsil, dura, orbit), or serous effusion
  - cytopenias (Hgb < 10 gm/dl, platelets < 100, 000/mm^3, ANC < 10^9/L) or leukemic phase (>50 X 10^9 cleaved lymphocytes/L).
- Stage III to IV [3]
- No contraindications to receiving corticosteroids, anthracyclines or INTRON®A.
- Seronegative for HIV
- No prior malignancies other than skin cancer
- No history of cardiac disease (heart failure, infarction within 6 months or arrhythmias),

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[2] Certain patients with other histologies listed in the translated original protocol were not included or were censored in this submission

[3] Ann Arbor staging criteria

uncontrolled diabetes, kidney or liver failure, non-compliance with monitoring

Treatment Plan

All patients were permitted to receive standard antiemetics in conjunction with chemotherapy. Patients randomized to chemoimmunotherapy (INTRON®A) received prophylactic paracetamol (acetaminophen-type antipyretic) 1000 mg PO given concurrently with the INTRON®A injections.

TABLE 1. Treatment Plan According to Study Arm

Drug	CHVP	CHVP plus INTRON®A
	Dose	
Cyclophosphamide Doxorubicin Teniposide (VM-26) Prednisone	600 mg/m^2 IV day 1 25 mg/m^2 IV day 1 40 mg/m^2 IV day 1 40 mg/m^2 PO d 1-5	600 mg/m^2 IV day 1 25 mg/m^2 IV day 1 40 mg/m^2 IV day 1 40 mg/m^2 PO day 1 through 5
INTRON®A	None	IFN α 5 MIU SQ TIW

CHVP was to be administered every 28 days during cycles 1 through 6 (induction). Patients with stable or responding disease after 6 cycles continued treatment for the next 12 months (maintenance) and received CHVP every 56 days for an additional 6 cycles (cycles 7 - 12). INTRON® A was administered for the duration of chemotherapy (up to 18 months).

Dose Modifications

- CHVP withheld for ≥ grade 2 hematologic toxicity (ANC < 1500/mm^3 or platelets < 75,000/mm^3)
- INTRON®A withheld for ≥ grade 3 hematologic toxicity (ANC < 1000/mm^3) and if grade 2 neutropenia occurred (1500/mm^3 > ANC > 1000/mm^3), the dose of INTRON®A was reduced by 50% (to 2.5 MIU). INTRON®A could be escalated up to 5 MIU after the neutropenia had resolved.
- INTRON®A permanently discontinued for grade 4 toxicities of SGOT > 5 x the upper limit of normal or serum creatinine > 2 mg/dl.

Supportive care

Standard medical care with antibiotics or other treatments for fevers, febrile neutropenia or infections, however no experimental treatments was permitted during the study. Treatment with hematopoietic growth factors (HGF) was not specifically addressed in the protocol; there were no approved HGFs in Europe during the study period and the sponsor has stated that no patient received HGFs. Listings of the concomitant care or medications was not required and was not submitted with this licensing supplement.

Monitoring

1. Baseline: comprehensive H&P, performance status[4], clinical and pathological staging[5], and laboratory assessment[6]. There was no requirement for assessment of tumor response with a single, consistent radiologic modality.
   All patients were to undergo lymph node biopsy prior to study entry. Histologic diagnosis was confirmed by a local and regional hematopathologist, then by the study pathologist - ——————————— In the event that the local and study pathologist disagreed on the diagnosis, the pathology was reviewed by an additional "regional" pathologist. If a consensus diagnosis of either FSCC or FM NHL was not reached, the patient was deemed ineligible.
2. During therapy
   - Complete blood count was obtained weekly for the first cycle, every 15 days during cycles 2 through 6 and monthly during cycles 6 through 12.
   - Chemistry, renal and liver function panels monthly for 18 months
   - Physical examination (PE) months 1, 2, 4, 5 (cycles 1, 2, 4, 5) and months 7, 8, 10, 11, 13, 14, 16, 17 (cycles 7, 8, 10, 11 and off month)
   - Tumor restaging by PE and/or radiographic studies every 3 months and at end of treatment; BM biopsies performed every 6 months and end of treatment
   - Clinically suspicious nodes were biopsied as clinically indicated
3. Follow-up assessments
   Evaluations for tumor response and survival performed every 6 months

Definitions

Complete response (CR): disappearance of all identifiable sites of disease including bone marrow

Partial response (PR)[7]: 50% reduction of the largest diameter of each identifiable site of disease or CR for all measurable lesions with residual bone marrow involvement

Minor regression (MR): ≥25% , < 50% tumor regression

Stabilization (SD): tumor regression < 25% or < 25% increase in marker lesions,

Progression (PD): increase of > 25% in marker lesions from baseline measurements or new disease sites

N.B. Case report forms (CRF) captured baseline clinical assessment of nodal size as a checklist

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[4] Performance status and adverse event severity grading utilized WHO scales

[5] physical examination, bone marrow biopsy, and radiographic scans (abdominal lymphangiogram, ultrasound or CT, mediastinal evaluation by chest x-ray or CT) for tumor measurement

[6] chemistry panel, CBC and coagulation studies

[7] The definition of PR was based upon greatest diameter, rather than area (cross-product of perpendicular diameters) and required a 50% reduction in all measurable lesions, rather than 50% reduction in the sum of the perpendicular diameters.

with 3 categories: normal, ≤3 cm, or > 3 cm. and baseline radiographic assessment as one of the following: normal, ≤ 7 cm and >7 cm. (See attachment A1)

CRF for subsequent assessments were in checklist format: response criteria for nodal disease captured as: CR, PR > 50%, PR < 50%, SD and PD. "B symptoms" and neutropenia <1000/mm^3 were recorded as "present" or "absent". (Attachment A2) [8]

Overall survival (OS) was measured from the date of randomization to the date of death or censored at the date of last follow-up

Progression-free survival (PFS) was measured from the date of randomization to the date of death or relapse or censored at the date of last follow up visit

Analytic Plan

The primary efficacy endpoint was prospectively defined in the translated protocol as comparison of progression-free survival. The sample size was based upon a 30-month progression-free survival. The analysis, to be performed after a "duration of inclusion of 3 years" with 150 patients per group, would allow the detection of a projected 20% difference in PFS with an alpha of 0.05 and power of 90%, using a one-tailed test. Secondary endpoints included comparison of OS between the two arms, and assessment of PFS at 18 months, OS at 3 and 5 years, overall response rate, complete and partial response rates, and response rates at one year in each of the two study arms. OS and PFS estimates were to be performed using the product limit method (Kaplan-Meier). The log rank test was used to detect any potential differences between the median OS or PFS between the 2 treatment groups. The PFS rates at 18 months and 3 years and the OS rates at 3 and 5 years were compared using the Fisher's Exact test. To assess the potential impact of baseline characteristics on the PFS and OS, analysis with the Cox's proportional hazards model using the stepwise method was performed by including the potential prognostic factors of: sex, age, PS, Ann Arbor stage, bone marrow involvement, systemic symptoms, number of extranodal sites, serum LDH and body surface area.

The analytic plan stipulated that a maximum of 5 interim analyses (every 18 months) would be performed. The primary efficacy endpoint would be considered statistically significant only if the associated p value (by Pocock's method) was ≤ 0.02. For the supplementary analyses based on the Cox's proportional hazards analysis, the conventional level of significance (0.05) was used. No early stopping criteria were specified in the protocol.

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[8] Since actual values were not recorded, verification of response rate required review of primary records; data were not available for 7 patients who underwent treatment.

Results

Quality of the data set
FDA performed on-site inspections at three study sites. The results of the bioresearch monitoring inspections lead to an assessment that the submitted data can be considered reliable and accurate; only non-substantive deviations from the protocol were reported from one site.

Summary
A total of 273 high tumor burden patients entered and were randomly assigned (1:1) to CHVP (n=135) or CHVP plus INTRON®A (N=138), from October, 1986 to June, 1991. The first interim analysis was scheduled for March 1, 1989, but was not performed until January, 1992, when 200 patients had completed the induction course. Following the publication of the results of this study (13), Schering contacted the study coordinator and requested access to the database to submit in support of this application.

The sponsor, Schering-Plough, in conjunction with the study coordinator, performed a two stage review of the data set. In the first stage, the data for 100% of the recorded variables (on the CRF) for a subset at 30 patients at 5 centers were verified against primary source documents. In the second stage, a review was conducted in 259 subjects for whom primary records could be located, for verification and updated information of 20 relevant variables (efficacy endpoints and collection of additional safety information). Verification of the data set against primary records revealed errors in 4% of the baseline variables, 7% of the treatment or response variables and 3% of the follow up survival variables. The sponsor's database, submitted to the FDA, incorporates the correct information for all verified data and thus differs slightly from the GELF database.

Patient disposition and population subset
A total of 273 patients were registered and randomized in this study and constitute the intent-to-treat (ITT) population. Eight patients did not receive any treatment; 5 of these patients were randomized to CHVP arm and 3 were randomized to CHVP + INTRON®A[9]. The remaining 265 patients who initiated treatment constitute the modified ITT population. There were 23 patients (11 in the CHVP arm and 12 in the CHVP +INTRON®A arm) who were determined on pathologic review to be ineligible (histologic diagnosis other than FSCC or FM NHL) following initiation of treatment. [10] The GELF cooperative group did not focus data collection or analyze the results of the 8 untreated subjects or the 23 incorrectly diagnosed subjects. The efficacy subset (n=242) utilized by GELF was derived by exclusion of these 31 patients from the ITT population. Dosing information is complete only for the efficacy subset. See Figure 2

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[9] Reasons for not proceeding to treatment were: ineligible histologic diagnosis (n=3), did not meet criteria for high tumor burden (n=3), incomplete study data (n=1), and explanatory information not available (n=1)

[10] FL, diffuse NHL, lymphomatous polyposis, other cancers or diagnosis, problem with pathology specimens, lymphoid hyperplasia

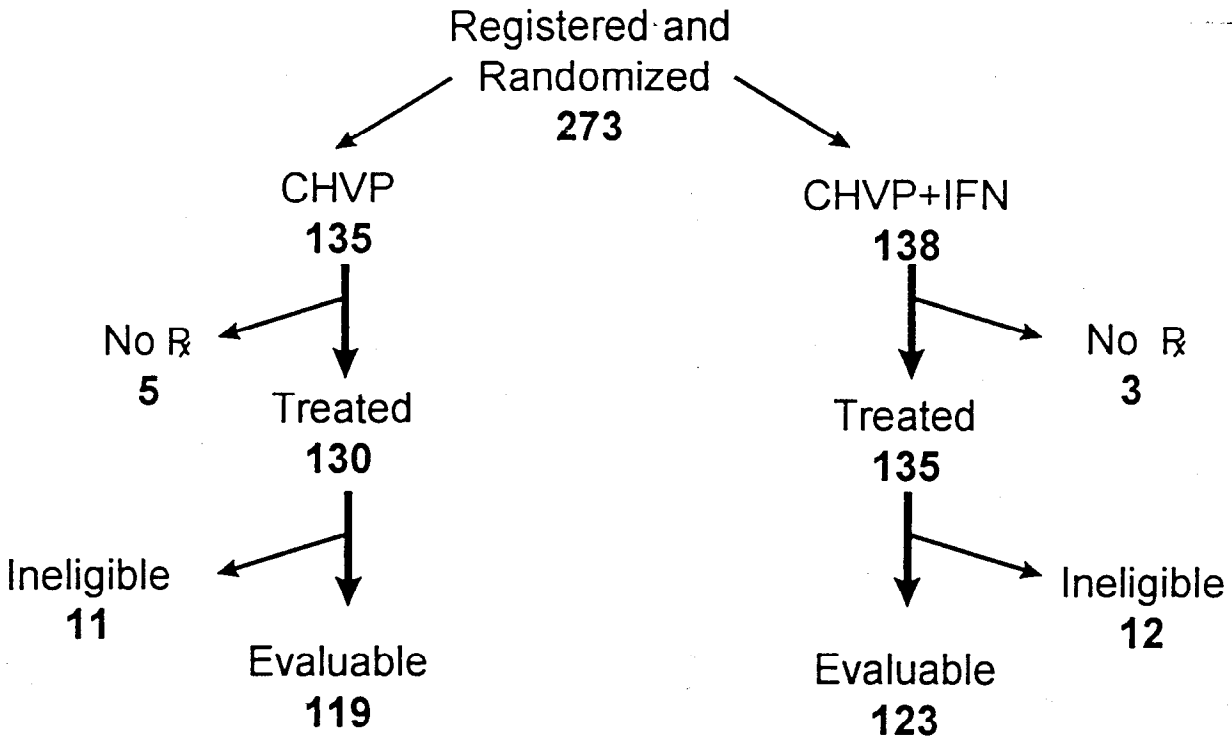

Figure 2 Patients disposition

Three of the nine participating centers that enrolled 10 or more patients accounted for approximately two-thirds (19 of 31) of the ineligible patients. These were: Center 14 (8 of 15 registered patients excluded), Center 15 (4 of 12 registered patients excluded), and Center 20 (7 of 28 registered patients excluded).

Table 2 provides information on the disposition of all 273 patients registered in the study. Sixty-five (48%) patients randomized to CHVP and 105 (76%) patients randomized to CHVP +INTRON®A completed all planned treatment cycles. The remaining patients failed to complete planned treatment for disease progression during treatment (38% *vs* 17%, CHVP *vs* CHVP +INTRON®A) or withdrawal for a variety of reasons (10% *vs* 5%, CHVP *vs* CHVP + INTRON®A), listed below.

TABLE 2. Completion of planned treatment		
Outcome of planned treatment	CHVP n=135 # subjects (%)	CHVP plus INTRON®A n=138 # subjects (%)
Completed therapy	65 (48%)	105 (76%)
Disease Progression/off study¶	51 (38%)	23 (17%)
Treatment Discontinued	14 (10%)	7 (5%)
Adverse Event	2	3
Regimen Changed*	3	2
Noncompliance†	7	0
Lost to follow up	0	1
Death	2	1
Treatment never initiated	5 (4%)	3 (2%)

¶ Includes 8 ineligible patients who relapsed (4 in each arm)

* 5 ineligible patients (based on pathologic review) who discontinued treatment and began alternative therapy.

† includes 4 patients who refused additional treatment

Comparability of the study arms

The study arms were well balanced for measures of disease burden, histologic subtype of disease, and other baseline entry variables. There were no significant differences with regard to any of these variables (see Table 3). In addition to those listed below, the median time from diagnosis to randomization (18 *vs* 17.5 days) and from randomization to treatment (2 *vs* 3 days) were similar for the CHVP and CHVP +INTRON®A arms, respectively.

TABLE 3. Comparability of Baseline Variables Between Study Arms		
Parameter	CHVP n=135 # subjects (%)	CHVP plus INTRON®A n=138 # subjects (%)
Mean age ± S.D.(yrs)	52 ± 11	52 ± 11
Gender (M: F)	70:65	78 :60
Mass > 7 cm	74 (55)	79 (57)
≥ 3 Sites of Disease	32 (24)	34 (25)
B Symptoms	34 (25)	42 (30)
Splenomegaly	12 (9)	17 (12)
Lymphocytes > 50,000/mm^3	9 (7)	10 (7)
Single Criteria (except B sx)	69 (51)	62 (45)
B Symptoms alone	11(8)	12 (9)
FSCC (large cells <5%)	24 (18)	28 (20)
FM, ≥ 5 to 15% large cells	66 (49)	63 (46)
FM, >15 to 50% large cells	16 (12)	22 (16)
Heterogeneous†	17 (13)	11 (8)
Other	12 (9)	14 (10)
Ann Arbor Stage		
II	4 (3%)	5 (4%)
III	20 (15)	23 (17)
IV	106 (79)	107 (78)
NOS	5 (4)	3 (2)

† node contained follicles of small cleaved cells and of mixed large and small cleaved cells

Treatment administered

The majority of patients in both arms received 80% or more of the intended dose intensity (as measured in mg/m^2/week), however, patients in the CHVP arm were more likely to receive 100% of the planned dose intensity. Information on doses of individual drug delivered were available only for the efficacy subset identified by GELF, 119 patients in the CHVP arm and 123 patients in the CHVP +INTRON®A arm. For the majority of patients, dose intensity for all chemotherapeutic agents was decreased by the same relative amount because the protocol required delay in therapy rather than dose reduction in the event of hematologic toxicity. In a few subjects, the dose intensity of a single drug was lower disproportionately as compared to the rest of the regimen; while no specific information was provided, it was assumed that in these cases, reduction or discontinuation of the drug was the result of a particular drug-associated treatment-related toxicity (*e.g.*, cardiac dysfunction).

During the initial 6 months of treatment (induction period), there were 17 patients in the CHVP arm and 24 in the CHVP +INTRON®A arm who had delay in treatment (20 and 32 cycles which were delayed for CHVP and CHVP +INTRON®A, respectively). During the subsequent 12

months (cycles 7-12 or maintenance therapy), there were again 24 instances in which chemotherapy cycles were delayed among 17 patients in the CHVP arm and 39 instances in which chemotherapy cycles were delayed among 28 patients in the CHVP +INTRON®A arm. In addition to a lower incidence in the proportion of patients who experienced a delay in treatment, the length of time for which treatment was delayed was also generally shorter in the CHVP arm. Eight percent of patients in both arms experienced a delay in at least one cycle of planned therapy of up to 4 weeks, however 7% of patients in the CHVP arm were delayed ≥ 4 weeks for at least one cycle as compared to 13% of patients in the CHVP +INTRON®A arm.

In the CHVP +INTRON®A arm, there was also modification of the INTRON®A dose. Eighty-three (62%) patients received 100% of the planned dose intensity of INTRON®A over the 18 months of treatment. One hundred twenty-three (92%) received ≥80% of planned dose intensity. There were 55 occasions among 39 (29%) patients where INTRON®A dosing was interrupted and 57 occasions among 17 patients where the dose of INTRON®A was modified. The most common reason cited for modification or temporary interruption of INTRON®A dosing was neutropenia. There were 14 patients (10%) for whom INTRON®A was permanently discontinued; these patients remained on study receiving CHVP alone. Two patients refused to receive INTRON®A therapy.

Efficacy Results

The primary efficacy endpoint, PFS at approximately 3 years (30 months) in the modified ITT population, demonstrated a 19% improvement (48% vs. 29%, p= 0.002, Fisher's exact test), consistent with the projected results and goals of the study. The results of this and additional analyses (median PFS and median OS) are reported for the modified ITT population (n=265) in Table 4. Both median PFS and median OS were significantly prolonged in patients randomized to the CHVP +INTRON®A arm. There is one patient (CHVP +INTRON®A) for whom survival status with less than 3 years follow-up was unknown. Based on continued follow-up through May 15, 1996, there were 112 (86%) patients in the CHVP arm and 100 (75%) patients in the CHVP +INTRON®A arm who experienced disease progression. Sixty-eight (52%) patients had died and 13 (10%) were alive with less than five years of follow-up in the CHVP arm, as compared to 49 (36%) patient deaths and 20 (15%) of patients alive with less than 5 years of follow-up in the CHVP +INTRON®A arm. The Kaplan-Meier curves generated for progression-free (Figure 3) and overall (Figure 4) survival are shown below.

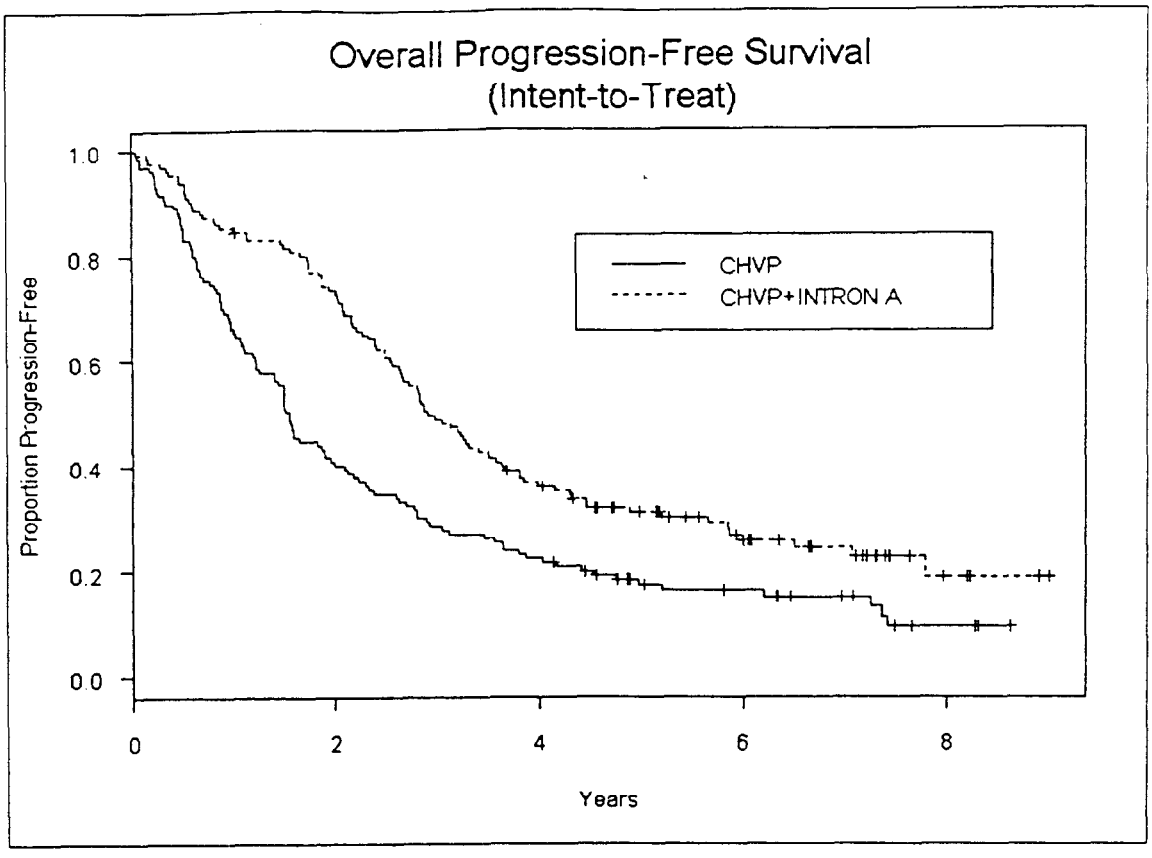

Figure 3

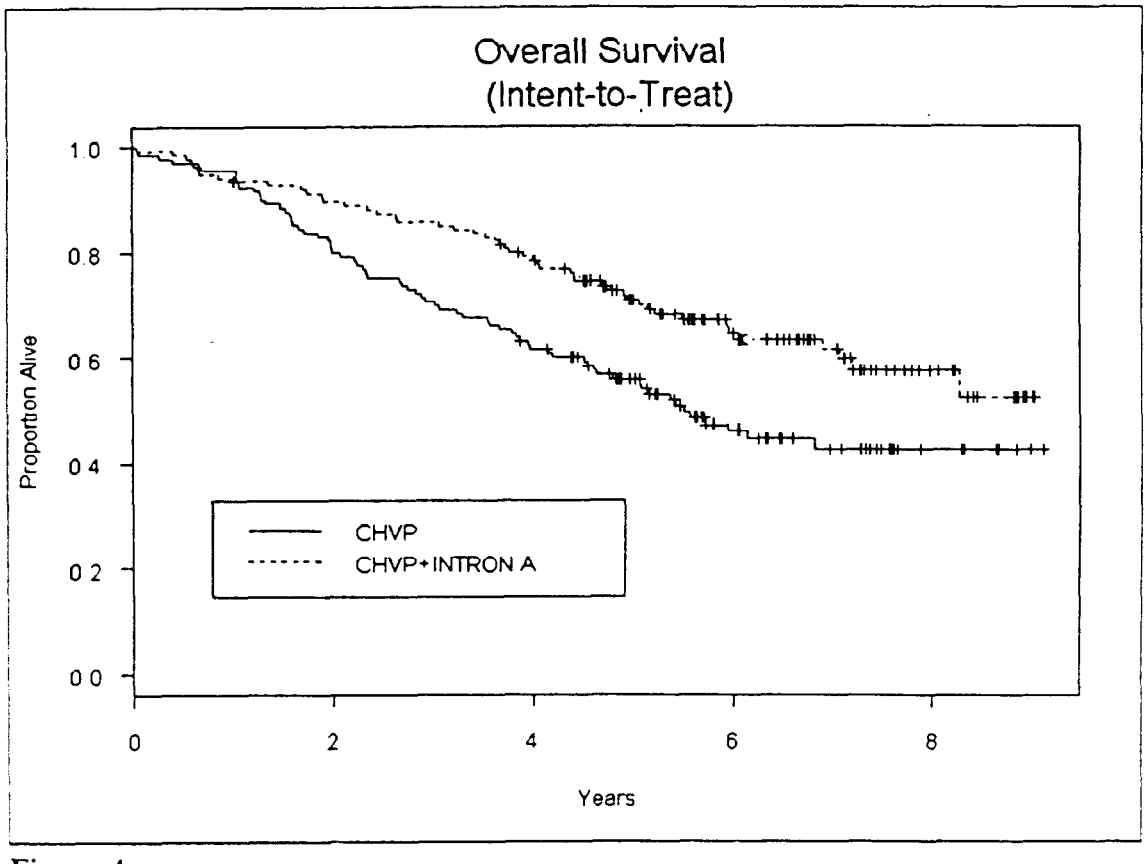

Figure 4

TABLE 4. Efficacy Endpoints			
Efficacy Variable	CHVP n=130	CHVP + INTRON®A n=135	P- value
3 yr PFS	29%	48%	0.002†
# of Pts w/ Progression	112	100	0.014¶
Median PFS (95% CI)	1.5 years (1.2, 2.)	2.9 years (2.6, 3.6)	0.0001§
Median OS	5.5 years	Not Reached	0.004§

† Fisher's exact test

¶ Chi-square test

§ Log-rank test (nominal p-values, no adjustment for multiplicity)

A recent update of the results of this trial for the efficacy subset (n=242) were published. In that update, the median PFS was reported to be 1.55 yrs vs.2.84 yrs and the median OS was reported to be 5.1 yrs *vs* 6.9 yrs, for the CHVP and CHVP +INTRON®A arms, respectively (14).

As noted, the patients receiving CHVP, were more likely to receive 100% of the intended doses (100% planned dose intensity) of the chemotherapeutic agents. A potential confounding factor in evaluating the survival benefit of CHVP +INTRON®A is the potential impact of lower dose-intensity leading to a lower rate of treatment-related mortality in the CHVP +INTRON®A arm. An analysis was performed to evaluate survival in patients receiving ≥ 100% of planned dose intensity (DI) and in those receiving <100% of planned DI. In both subsets (≥100% DI and <100% DI, patients randomized to CHVP +INTRON®A had a survival advantage. The magnitude of the survival benefit was greater in patients receiving less than 100% DI.

Secondary analyses

Secondary analyses comparing the PFS rates at 18 months and at 3 years and the survival rates at 3 years in patients who initiated treatment (n=265) are shown in Table 5, below. At each time point, the PFS and OS rates were significantly better in patients who were randomized to the CHVP + I arm. FDA chose to calculate only the overall survival rate at 3 years. The overall survival rate at 5 years was not calculated because of concerns regarding completeness and maturity of the data (10% and 15% of patients in each arm alive with less than 5 years follow-up). The PFS rates were approximately one-third higher at both 18 and 36 months and the survival rate was approximately 20% higher at three years for patients in the CHVP +INTRON®A group.

TABLE 5 Secondary Efficacy Endpoints: Survival Rates			
Survival Rates	CHVP n=130	CHVP plus INTRON®A n=135	P value§
PFS rate @ 18 months	53%	81%	<0.001
OS rate @ 3 years	71%	85%	0.012

§ Fisher's exact test (nominal p-values, not adjusted for multiplicity)

Additional analyses were performed to assess the consistency of effect on progression-free survival across centers. Among the nine centers that enrolled 10 or more patients, PFS rates at 3 years were higher for the CHVP + I arm in eight of these nine centers. Of note, the center where the control (CHVP arm) had a higher 3 year PFS rate was also the highest accruing center, enrolling 44 of the 265 patients who received treatment.

Assessment of overall, complete and partial response rates were assessed in a subset of 258 patients for whom verification of response from the primary records could be obtained by the sponsor. The overall (90% *vs* 74%) and complete response rates (56% *vs* 32%) were significantly higher for patients randomized to the CHVP +INTRON®A arm, whereas the partial response rate was lower (34% vs. 42%). After six months of induction therapy, 73% of patients in the CHVP +INTRON®A arm and 58% in the CHVP arm had achieved objective clinical responses, but only one-quarter and one-fifth, respectively were complete responses. After a total of 18 months of therapy (an additional 12 months of maintenance therapy), the overall response rates were similar, however slightly more than half of the response were complete responses. This pattern of continuing and improving response was similar in the two study arms.

TABLE 6. Secondary Efficacy Variables Response Rates			
Response Rates	CHVP N=125	CHVP + INTRON®A N=133	P value§
ORR	**74%**	**90%**	**< 0.001**
ORR @ 6 mos	58%	73%	0.01
ORR @ 18 mos	46%	75 %	< 0.001
CR Rate	**32%**	**56%**	**<0.001**
CR @6 mos	12%	19%	0.2
CR @18 mos	25%	46%	< 0.001
PR Rate	**42%**	**34%**	**0.2**
PR @6 mos	46%	54%	0.2
PR @ 18 mos	22%	29%	0.2

§ Fisher's exact test (nominal p-values, not adjusted for multiplicity)

Safety Results

General

The majority of the adverse events observed were reported in both study arms. The incidence of toxicities which are known to be related to the type I interferons, including INTRON®A, were either higher and/or more severe in the CHVP +INTRON®A arm than in the CHVP-treated patients. These toxicities included constitutional symptoms (fever, headache, flu-syndrome, rigors, malaise/asthenia, anorexia, and weight loss), liver function abnormalities, myelosuppression, neurologic and psychiatric events. Table 7 below lists the adverse events which occurred significantly more often in those randomized to the CHVP-INTRON®A arm as compared to those in the CHVP arm. The significantly higher rates of dyspnea (14% *vs* 5%), and polyuria (10% *vs* 2%) have not been observed with the use of interferon in other approved indications. The incidence of severe adverse events other than hematologic toxicity, was generally low and no statistically significant differences were observed between the two arms for grade 3/4 non-hematologic toxicity. However, the small number of serious pulmonary, hepatic and neuropsychiatric events observed in patients randomized to CHVP +INTRON®A, are of concern and might mandate more specific precautions for use the use of INTRON®A in this setting. With regard to serious pulmonary events, there was a single severe event (pleural effusion) in the CHVP compared to 11 severe events (total number of subjects unclear) in the CHVP +INTRON®A arm; these included severe dyspnea (n=5), respiratory insufficiency (n=2), bronchitis (n=2), and 1 episode each of severe pneumonitis, pleural effusion, pulmonary infection, and hypoventilation. All pulmonary toxicity resolved without aggressive medical intervention and no subject was reported to have discontinued INTRON®A for these pulmonary toxicities. Six patients developed serious hepatotoxicity and all were in the CHVP +INTRON®A arm. Three of these subjects, further described below, had underlying hepatic dysfunction, including viral Hepatitis B in two subjects and alcoholic cirrhosis in the third.

TABLE 7. INTRON®A Related Adverse Events

Event	CHVP n=130	CHVP + INTRON®A n=135
Any Skin AE*	30%	43%
Abnormal Liver Enzymes**	9%	24%
Anorexia**	8%	21%
Dyspnea**	5%	14%
Polyuria**	2%	10%

*P-value less than 0.1, **P-value less than 0.05

Neurologic and Neuropsychiatric Adverse Events

The comparative incidence of neurologic and neuropsychiatric adverse events are provided in Table 8 below. Neuropsychiatric events, including suicidal ideation (in a variety of clinical

settings) and neurologic toxicities, including paresthesias (in the setting of AIDS-related Kaposi's sarcoma) have been previously reported. The factors which are associated with an increased risk for development or exacerbation of depression and/or suicidal ideation have not been fully investigated. At the time of the conduct of the study, the association between depression with or without suicide and type I interferons had been described but the incidence of serious events was not clear. The protocol did contain an exclusion criterion for psychiatric disorders which would preclude the use of INTRON®A. From these data and those obtained in the setting of AIDS-related KS, it appears that INTRON®A has additive or synergistic effects in the setting of disease-related or treatment-induced peripheral neuropathy.

TABLE 8 Neuropsychiatric/Neurologic Adverse Events

Event	CHVP n=132	CHVP + INTRON®A n=136
Amnesia	0	1%
Anxiety	19%	9%
Depression	7%	9%
Insomnia	5%	4%
Paresthesia†	6%	13%
Psychosis	0	1%
Suicides	0	2%
Vertigo	4%	8%

† p=0.062, Fisher's exact test

Hematologic Adverse Events

The incidence of hematologic events affecting all three lineages was increased in patients randomized to the CHVP +INTRON®A arm. The increased incidence of anemia (13% *vs* 2%) and thrombocytopenia (8% *vs* 3%) was due to an increase in mild to moderate toxicities, with few serious events of anemia and thrombocytopenia, however neutropenia, when it occurred in either arm, was primarily grade 3 or 4 in severity and significantly higher in patients randomized to CHVP +INTRON®A (34% *vs* 6%). This higher rate of serious neutropenia led to chemotherapy dose delays in 32% of CHVP +INTRON®A patients and INTRON®A dose reduction or interruption in 29% and 12% of patients, respectively. The incidence of infections observed during periods of neutropenia was higher in patients randomized to CHVP +INTRON®A, with 2 events observed among patients in the CHVP arm (1 patient each with sepsis and UTI in the setting of neutropenia) compared to 8 events among patients in the CHVP +INTRON®A arm. These events included viral infection, tonsillitis, otitis, bronchitis, pulmonary infection and infection (not otherwise specified) in 1 patient each and 2 patients with pharyngitis. The only patient reported to require hospitalization was a patient with pharyngitis and

neutropenia on the CHVP +INTRON®A arm.

TABLE 9. Hematologic Toxicities						
Lineage affected	All Grades			Grade 3 and 4		
	CHVP n=130	CHVP + I n=135	*P value	CHVP n=130	CHVP +I n=135	*P value
Neutropenia	8%	36%	<0.0001	6%	34%	<0.0001
Thrombocytopenia	2%	13%	0.003	1%	1%	1.00
Anemia	3%	8%	0.1	2%	3%	0.7

* Fisher's exact test

Patient deaths on study

There were 5 deaths reported during treatment or within 30 days of the last dose of study drug. Two patients in the CHVP arm were reported to have unwitnessed sudden death at home. One patient was found dead 2 weeks after chemotherapy; although the cause of death was attributed to pulmonary embolus, no post mortem examination was obtained. The second patient had a history of angina that was not active at the time he entered the trial. Approximately 3 weeks after his first cycle of CHVP, he was found dead at home. Neither of these deaths were rated by the clinical investigator as related to treatment.

There were 3 deaths in the patients randomized to CHVP plus INTRON®A. Two patients with a history of depression committed suicide during the trial. One patient committed suicide day 10 of cycle 1 after receiving a single dose of INTRON®A. The second patient killed himself approximately 3 weeks after progression had been diagnosed during his 6 month treatment evaluation. The patient's family reported that his depression had worsened significantly after he was notified of his progression. The last patient had clinical evidence of disease progression after cycle 5. Although the biopsy confirmed transformation into large cell NHL, the patient received cycle 6 on schedule. Approximately 3 weeks after this treatment the patient expired from "lymphoma with transformation."

Discontinuation of one or more study drugs due to serious and/or intolerable adverse events

Doxorubicin-related events

- Cardiac toxicity was reported in 5 patients. This included non-fatal myocardial infarction in one patient and decreased left ventricular ejection fraction in four patients. Doxorubicin was discontinued in the subject with infarction and three of the four with decreased ejection fraction, while other study medications were continued without further cardiac events. In the remaining patient, randomized to CHVP + INTRON®A, the physician chose to discontinue all therapy.
- Cutaneous necrosis secondary to doxorubicin extravasation (n=1, CHVP).

VM-26-related events

- 3 patients suffered anaphylactoid reactions to VM-26, which was permanently

discontinued (CHVP [n=1]; CHVP +INTRON®A [n=2]).

Cyclophosphamide-related events

- Acute pneumonitis after cycle 10 requiring steroid treatment, attributed to cyclophosphamide which was permanently discontinued (n=1); subject completed therapy (C11 & C12 administered without cyclophosphamide)

INTRON®A-related events

- Psychotic episode occurred in one patient receiving CHVP +INTRON®A and concurrent prednisone (70 mg per day; medication error). INTRON®A was discontinued with resolution of symptoms. INTRON®A was resumed then discontinued permanently when psychosis recurred.
- INTRON®A was permanently discontinued in three patients who developed elevated liver function tests. Two of these subjects were known to have cirrhosis secondary to ethanol abuse and/or hepatitis B at the time of study entry. A diagnosis of hepatitis B was made in the third patient during the evaluation of the transaminitis. Liver function tests improved after cessation of INTRON®A. Type I interferons are known to cause acute exacerbation and, in the setting of marginal functional hepatic reserve, acute decompensation in patients with viral hepatitis.
- One patient with pre-existing ankylosing spondylitis experienced exacerbation of symptoms, which improved after discontinuation of INTRON®A. Patient tolerated CHVP alone without further exacerbation. Flare or exacerbation of pre-existing connective tissue disorders following type I interferons has been reported (21).
- INTRON®A was permanently discontinued in 5 patients for intolerable asthenia or anorexia
- INTRON®A was permanently discontinued after cycle 2 for severe "flu" symptoms in one patient.

B. Literature review

Studies of interferon in combination with chemotherapy

When possible the data that follow were obtained from the original publication. However, a recent review article of interferon in lymphoma (15) contained data not found in the original publication which was attributed to "personal communication" and where these data represent an update of the original publication, this source was used.

ECOG

Smalley *et.al.* (12, 16) reported the results of a randomized, open label, multicenter study of a four drug chemotherapeutic regimen alone or combined with recombinant interferon alfa-2a (Roferon®A) conducted by the Eastern Cooperative Oncology Group (ECOG) between 1985 and 1988. The eligibility criteria included previously untreated, stage III or IV NHL, with the

following subtypes: DWDL, NPDL, DPDL, NM, or NH[11]. Patients with DWDL and NPDL were eligible only if they had B symptoms, ≥2 nodes of >3 cm or 1 node of >5 cm in diameter, organ dysfunction, liver or lung involvement. Patients were randomized to receive the COPA regimen: [cyclophosphamide 600 mg/m^2 IV on day 1, vincristine (Oncovin) 1.2 mg/m^2 IV on day 1, prednisone 100 mg/m^2 PO on days 1 through 5, and doxorubicin (Adriamicin) 50 mg/m^2 on day 1 of each 28-days cycle,], or COPA with concurrent interferon alfa-2a (I-COPA) at a dose of 6 MU/m^2 IM on days 22 through 26 of each 28-days cycle. Patients with responding or stable disease received 8-10 cycles of treatment. The objectives of the study was to determine response rate, duration of response, time to treatment failure, overall survival and toxicity.

Two hundred ninety-one patients were enrolled; of these, 249 patient were evaluable (127 in the COPA group and 122 in the I-COPA group). The distribution of histologic subtype among the study participants was: NPDL 29%, NH 27%, DPDL 24%, NH 11% and DWDL 10% [approximately half, 56%, were of follicular low grade]. The median age was 57 years in the COPA group and 59 years in the I-COPA group. Twenty-nine percent of the patients in the COPA group achieved a CR, and 57% achieved a PR, for an overall response rate of 86%; the corresponding response rates in the I-COPA group were 32 % CR, 54% PR, for an ORR of 86%. At the time of publication, the median duration of complete response had not been reached in the I-COPA and was 1.7 years in the COPA group. Time to treatment failure at five years was 34% in the I-COPA arm *vs* 19% of the COPA arm. There was no significant difference in the overall survival in the two arms.

The incidence of infections was slightly higher in the COPA group, whereas the incidence of fever (2% *vs* 12%) and neurologic disorders (6% *vs* 10%) was higher in the I-COPA group. The incidence of neutropenia was similar (35% vs 34%), however patients in the I-COPA received 25% less cyclophosphamide and doxorubicin over the course of treatment.

St. Bartholomew's

The preliminary results of a randomized study conducted at three different sites in the UK was reported by Price *et.al.*(8). The study started in 1985 and accrual continuing at the time of the first publication. The eligibility criteria included previously untreated, follicular NHL, stage III or IV disease, with a clinical indication for treatment. Specifically, asymptomatic patients with stable disease were not eligible. Patients were randomized to receive single agent chlorambucil (10 mg daily, weeks 1-6, then daily weeks 9-10; 13-14; and 17-18) or chlorambucil (same dose and schedule) plus interferon alfa-2b (INTRON®A) at a dose of 2 x10^6 U/m^2 three times weekly by subcutaneous injection for 18 weeks. After the initial 18 weeks of treatment, responding patients underwent a second randomization to maintenance interferon alfa-2b for seven to twelve months or no further therapy.

Of the 124 patients entered, 108 were evaluable with a median follow-up of 30 months at the

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[11] Rappaport classification: DWDL (diffuse well-differentiated lymphoma), NPDL (nodular poorly differentiated lymphoma = FSCC), DPDL (diffuse poorly differentiated lymphoma), NM (nodular mixed = FM), (NL nodular histiocytic)

time of the initial publication. At that time, 49 patients had been randomized to receive chlorambucil plus interferon and 59 to chlorambucil alone. The overall and complete response rates to chlorambucil plus interferon were lower than for chlorambucil alone (ORR 55% vs. 71%; CR 16% vs. 25%). Of the eighty-one (81) patients with a complete, partial or minor response, eligible for the second randomization, 71 continued on study. In the initial publication, the remission duration in patients achieving a CR or PR was prolonged in patients receiving interferon during induction or for maintenance and there was no difference in survival at three years. The results of this study were updated in an abstract in 1996. The report describes results in 204 evaluable patients (100 chlorambucil and 104 chlorambucil plus interferon), with a median age of 52 years (range 25-81 years), 25% of whom had stage III and the remainder stage IV follicular lymphoma. One hundred twenty-six (126) patients achieved a CR or PR and one hundred eight of these patients went on to second randomization. The response rates were again slightly lower in the chlorambucil plus interferon group (74% vs. 84% ORR; 20% vs. 28% CR), and there were no differences in overall survival or time to progression, however, there was a significant difference ($p=0.04$) in response duration for patients in CR receiving interferon.

Information regarding adverse events are reported only in the original publication on 124 patients. The major toxicity, myelosuppression requiring dose modifications, was significantly more frequent in the combination arm than in the chlorambucil alone arm (62% vs. 16%, $p<0.01$). Additional toxicities included systemic interferon-related symptoms which required discontinuation of the drug in 8% of patients, and hemolytic anemia, seizure, and exacerbation of angina in one patient each.

CALGB

Peterson *et. al.* (7) reported in abstract format the results of a multicenter, randomized, open-label study of single alkylating agent therapy (cyclophosphamide) alone or in conjunction with interferon alfa 2b (INTRON® A) which accrued patients from Nov., 1986 to May, 1991. Patients with previously untreated, stage III or IV, FSCC or FM subtypes of NHL were eligible. Patients were randomized to initial treatment with cyclophosphamide 100 mg/m^2/day or cyclophosphamide 100 mg/m^2/day plus interferon 2 x 10^6 IU/m^2 TIW. Treatment continued for 3 months post documentation of partial or complete response. Responding patients underwent a second randomization to 2 years of maintenance interferon or observation.

Five hundred and eighty-one patients were registered and randomized; of these, 531 were evaluable. Only the results of the induction therapy were reported in the abstract. At the time of the abstract, the median followup was 2.7 years. Complete response rate was 45% in both groups with an ORR of 89% for cyclophosphamide and 84% for cyclophosphamide plus IFNα (15). The time to treatment failure was estimated to be 46% in the cyclophosphamide-interferon arm and 47% in the cyclophosphamide arm at 3 years. Estimated 3 year survival rates were respectively 78% and 80% and estimated 3-year response durations were 37% and 40% in the cyclophosphamide-interferon and cyclophosphamide arms, respectively.

The authors remarked that cyclophosphamide plus interferon was considerably more toxic. Granulocytopenia (<1000/mm^3) occurred in 57% of the interferon arm *vs* 29% of the

cyclophosphamide alone arm, and severe infections were reported in 9% and 5%, respectively. Thrombocytopenia, fever, neurotoxicity and other side effects were also significantly more common with the combination.

TABLE 11. Chemotherapy and Concurrent Interferon

Group	Chemotherapy	Survival	Failure-free survival
ECOG	COPA+IFN COPA	61% (5 years) 54% (5 years)	34% (5 years) 19% (5 years)
St.Bartholomew's	Chlb+IFN Chlb	75% (3 years) 75% (3 years)	60% (3 years) 49% (3 years)
CALGB/ECOG	Cyclo+IFN Cyclo	78% (3 years; estimated) 80% (3 years; estimated)	46% (est. 3 years) 47% (est. 3 years)
GELF	CHVP+IFN CHVP	85% (3 yrs) 71% (3 yrs)	48% (3 yrs) 29% (3 yrs)

Studies of interferon as maintenance

MD Anderson (MDACC)

In 1993 McLaughlin *et.al.* (6) reported the results of a prospective non-randomized study of interferon maintenance schedule after combination chemotherapy. Previously untreated patients with stage IV, DSL, FSCC, and FM subtypes of NHL were eligible; with the exception that DSL with 15,000 lymphocytes/mm^3 were excluded. Patients with low risk features were initially treated with an 8 week interferon regimen prior to chemotherapy; those with high-tumor burden went directly to combination chemotherapy. The chemotherapy regimen consisted of CHOP-Bleo for 9-18 months (cyclophosphamide 750 mg/m^2 IV on day 1, doxorubicin 50 mg/m^2 IV on day 1, vincristine 2 mg IV on day 1, prednisone 100 mg PO on days 1-5, bleomycin 15 U IV on day 1) every three weeks. Following chemotherapy, patients with residual disease could receive radiotherapy or daily interferon in an attempt to achieve a CR. Patients who achieved complete remission were to receive lymphoblastoid interferon, interferon alfa-n-1 (Wellferon®) three times weekly for 2 years. The authors compared the results of this trial to patients with stage IV low grade follicular lymphoma treated with identical therapy (CHOP-Bleo) at MDACC during an 8-year period preceding this trial.

Between 1982 and 1988, 139 patients were registered on the protocol, 127 patients were evaluable The median age was 54 years (range 25-83). The histologic findings included: diffuse small lymphocytic (14%), follicular small cleaved (61%), and follicular mixed lymphoma (24%). Of the 127 patients, 93 (73%) achieved a CR and 29 (23%) achieved a PR following all treatment There were 51 patients with low risk features who received interferon induction prior to chemotherapy; 49 of these were evaluable with a CR rate of 2% (n=1) and PR of 27% (n=13).

The overall survival at five years for patients with follicular lymphoma(n=109) was 73%. The failure free survival however was reported to be at five years 47%, whereas the historical control group of 96 patients had a 27% 5-year failure-free survival.

Fatigue was the most common toxicity (56%) and was severe in 13% of the patients. Other toxicities included myelosuppression, nasal congestion, weight loss, rash, confusion/involution, nausea. Involution or depression was severe in one patient. Dose reduction was necessary in 37% of the patients primarily because of unacceptable fatigue.

EORTC

The results of a prospective, randomized, multicenter study performed by the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Cooperative Group were reported in abstract format in 1995 by Hagenbeek *et. al.* (11).

A total of 347 patients with previously untreated, low grade, follicular NHL, stages III and IV were enrolled between October 1985 and November 1992. Patients received eight courses of CVP (cyclophosphamide 300 mg/m^2 PO on days 1-5, vincristine 1.4 mg/m^2 IV on day 1, and prednisone 40 mg PO on days 1-5) followed by radiotherapy for bulky disease or slow response. Responding and stable patients were randomized to receive either recombinant interferon alfa 2a (Roferon®A) 3 x 10^6 IU SC TIW for 1 year or no further treatment. Among the 347 patients enrolled, 253 of the 288 stable or responding patients (88%) were randomized to interferon maintenance (n=126) or no further therapy (n=127). With a median followup of 4 years, the median PFS was 34 months for IFN group and 22 months for the control arm (p=0.04) [reference 15]. There was no significant difference in survival between the groups. No information regarding toxicity was provided in the abstract.

German LGL study group

The results of a prospective, randomized, open-label study conducted by the German Low Grade Lymphoma Study Group were reported in abstract format in 1995 by Unterhalt *et.al.* (17). Patients with stage III and IV, follicle center lymphoma or mantle cell lymphoma were treated with cytoreductive therapy consisting of cyclophosphamide, vincristine and prednisone (COP) or prednimustine and mitoxantrone (PmM). Patients achieving a response to chemotherapy were eligible for randomization to interferon alfa until relapse or intolerable toxicity at a dose of 5 x 10^6 U/d TIW (adjusted to tolerance) or no treatment.

Between 1988 and 1995, a total of 503 patients were enrolled of whom 247 were randomized to IFN or observation. Ninety-one (18%) had follicle center lymphoma and 412 (82%) had mantle cell lymphoma of the 503 beginning treatment; characteristics of patients who were randomized for maintenance were not provided. This portion of the study was terminated based upon a significant advantage in disease-free survival estimated at 3 years in the first 142 patients (46% *vs* 22%, p=0.0048) for patients receiving maintenance interferon. The survival data were not mature and no information on survival was reported.

Adverse events, primarily fever, myalgia and fatigue, resulted dose reductions in 70% of

interferon-treated patients and discontinuation of interferon in 22% during the first 6 months.

Mexican Study Group

Avilés *et. al.* (18) reported in 1996 the results of a randomized study of maintenance interferon of patients achieving complete remission after an complex, combination chemotherapy regimen. The regimen consisted of two cycles of low dose methotrexate with leucovorin rescue, followed by two cycles of CEOP-Bleo (cyclophosphamide, epirubicin, vincristine, prednisone and bleomycin) given every three weeks, then six cycles of CVP (cyclophosphamide, vincristine and bleomycin) given at monthly intervals; consolidation radiotherapy could be administered to responding patients with residual disease. Only those patients achieving a complete remission to this regimen were eligible for entry into the maintenance protocol. Patients were randomized to interferon-alfa 2b (INTRON®A) 5 x10^6 U TIW for one year or observation.

Ninety-eight patients (65% of the 151 patients who received the MTX-CEOP-CVP regimen) achieved a CR and were randomized in this study; 48 were randomized to INTRON®A and 50 to observation. Eighty-eight (88) percent of those randomized to INTRON®A and 90% to observation had follicular small cleaved cell or follicular mixed histology. The proportions with stage IV disease (77% vs 80%), bulky disease (39% vs. 38%), marrow involvement (50% vs. 42%), and LDH >275 U/ml (46% vs. 50%) were similar for the INTRON®A and observation arms, respectively. he histologic findings included diffuse small lymphocyte, follicular small cell and follicular mixed NHL in stage III and IV, approximately half of the patients had bulky disease. The authors report the results at nine-years and provide Kaplan-Meier plots of the remission duration (equivalent to PFS in this population) and overall survival; the 5-year PFS and survival data provided in Table 12 are obtained from these plots. At the time of the report, the median follow-up was 69 months (range 46-90 months). The failure-free survival at nine years was reported to be 62% in the INTRON®A arm and 25% in the control group. The survival rate at nine years was 80% in the INTRON®A arm and 50% in the observation; the median survival in the observation was 6.1 years.

The authors reported that no patient discontinued INTRON®A due to toxicity, however, INTRON®A dosing was briefly interrupted for leukopenia (<4.0 x 10^9/L) in 10% of patients and for grade 1-2 thrombocytopenia in 12.5% of patients. Sixteen patients (33%) developed flu-like symptoms of WHO grade 1 which did not require dose reduction or interruption.

TABLE 12. Chemotherapy and Interferon Maintenance

Group	Chemotherapy	Survival	Failure-free survival
MD Anderson	CHOP+IFN CHOP	74% (5 yrs) 64% (5 yrs)	45% (5 yrs) 27% (5 yrs)
EORTC	CVP+IFN CVP	84% (3 yrs) 84% (3 yrs)	Median 2.8 yrs Median 1.8 yrs
German LGL Group	COP, PmM+IFN COP, PmM	Not stated	46% (3 yrs) 22% (3 yrs)
Mexican Study Group	MTX, CEOP-Bleo, CVP + IFN MTX, CEOP-Bleo, CVP	≈ 88% (5 yrs) ≈ 65% (5 yrs)	≈ 75% (5 yrs) ≈ 47% (5 yrs)

VI. Integrated Summary of Effectiveness

The information submitted and reviewed in support of the proposed new claim includes the results of a multicenter, randomized, controlled trial conducted by GELF and relevant published information from several randomized, controlled, open-label studies and one historically controlled study (MDACC) evaluating the impact of concurrent chemoimmunotherapy and/or the role of interferons as maintenance therapy in previously untreated, follicular subtypes of non-Hodgkin's lymphoma. In the GELF study, the addition of INTRON®A to CHVP resulted in significantly higher progression-free and overall survival, and in a higher overall and complete response rate to initial therapy. The finding of an advantage in progression-free survival in patients undergoing chemoimmunotherapy was also observed in a study of similar size conducted by ECOG (12) and in the preliminary report of a smaller study (8). There are several additional studies, evaluating the effects of interferon maintenance therapy in following chemotherapy induction have also observed an improvement in progression-free survival. In two large, randomized controlled studies of approximately 500 patients each, with randomization to a minimum of one year of interferon maintenance or no further therapy, improvements in median PFS (2.8 yr *vs* 1.8 yr) and 3-year PFS (46% *vs* 22%) were observed in patients receiving interferon maintenance as compared to no maintenance.

These results stand in contrast to the results of the largest randomized, controlled trial of chemoimmunotherapy induction conducted in patients with follicular NHL, in which Peterson reported no evidence of improvement in progression-free survival. One proposed explanation for the negative results of the CALGB study has been that the patient population was a better prognostic group than that studied by GELF or ECOG. Information provided in the published literature is incomplete and, thus it is difficult to compare patient characteristics across these studies. However enrollment of patients with high tumor burden through specific inclusion criteria, e g., symptomatic disease, extranodal disease or bulky sites of disease, were components of the GELF, ECOG, and St. Bartholomew studies. Given the negative findings of the CALGB study and the specific exclusion of patients with low tumor burden from the GELF study, the benefit of interferon in prolongation of time to progression appears to be limited, at best, to a

high risk subset of patients with follicular NHL.

Other findings of the GELF study have not been well supported by the published literature. The majority of studies have failed to demonstrate a survival advantage. These findings are consistent with the general experience in follicular lymphoma in which a variety of strategies have failed to demonstrate a positive effect on survival. There is only one study which has also shown a survival advantage for interferon as maintenance therapy. This study, reported by Avilés, is small (n=98). In addition, the survival and progression-free survival rates in both the interferon-maintenance and control groups in the Mexican trial are clearly outside the range reported by all the other groups noted above. Based on these reported differences, it appears that the study population in the study reported by Avilés is not comparable to GELF or the other publications cited and the results of this study should not be extrapolated or considered to support this proposed indication.

Similarly, although an improvement in overall and complete response rates in patients receiving interferon were observed in the GELF study, all studies reported (CALGB, ECOG, St. Bart's) which have evaluated the concomitant use of chemotherapy and interferon have reported no difference in response rates between the chemoimmunotherapy and chemotherapy.

VII. Integrated Summary of Safety

The adverse event profile in the GELF study is consistent with previously described adverse effects of alpha interferons. However, the incidence of myelosuppression (manifested predominantly by neutropenia), hepatic dysfunction, paresthesias, pulmonary dysfunction, anorexia, cutaneous reactions, and polyuria were significantly increased in subjects receiving chemoimmunotherapy in the GELF study, which appear to be the result of overlapping or potentially synergistic toxicities.

In the GELF study, as well as the trials conducted by CALGB and St. Bartholomew, significant increase in incidence of grade 3 and 4 myelosuppression in the chemoimmunotherapy arm (as compared to chemotherapy alone) was observed. The incidence of severe myelosuppression in the ECOG study was not different in the two treatment arms, as a result of frequent dose reduction, as manifested by a 25% lower dose intensity per cycle of cyclophosphamide (77% *vs* 97%) and doxorubicin (75% *vs* 95%) in the I-COPA arm. The increased myelosuppression did not appear to be associated with an increase in clinical sequelae (infections, bleeding, or transfusions).

At this dose and schedule, serious toxicities, including depression and completed suicide were observed in the GELF and in the study conducted at MD Anderson Cancer Center (13% incidence of severe depression). Neurologic toxicities (not further specified) were also higher in the I-COPA arm and compared to the COPA arm (10% *vs* 6%). In addition, one patient in the MDACC study discontinued treatment due to paresthesias (1.4%) and seizure was reported in one patient in the St. Bartholomew study (2%). The incidence and type of neurologic toxicities are of consequence in weighing the value of the progression-free survival advantage of chemoimmunotherapy.

The incidence of other constitutional symptoms, such as fever, chills, anorexia, and fatigue, were higher in patients receiving chemoimmunotherapy. There were no prospective attempts to evaluate the impact of these common symptoms on the quality of life of patients receiving immunotherapy. Given that all of these studies were open-label studies, assessment of such data would be difficult in any case.

VIII. Summary

The results of the GELF study, as well as several randomized, controlled studies of chemoimmunotherapy and interferon as maintenance therapy, consistently have shown an improvement in progression-free survival in patients with follicular lymphoma. The single exception is a study conducted in a general, rather than high tumor burden population, which suggests that the benefits of interferon in this setting are limited to a subgroup of patients with follicular small cleaved cell and follicular mixed non-Hodgkin lymphoma. The findings of improved survival and response rates in the GELF study are not supported by the published literature. The toxicity of chemoimmunotherapy for initial treatment of low grade, high-tumor burden, follicular NHL carries with it considerable, though not intolerable toxicities. The spectrum of these toxicities would warrant close monitoring, particularly for myelosuppression, hepatic function, and neurologic/psychiatric effects.

One concern regarding the application of the results of the GELF study relate to the differences in combination regimen used and the duration of therapy, both of which differ significantly for that commonly employed in the United States. The use of interferon does impact the delivery of even modestly myelotoxic therapy. In earlier studies by ECOG, the cycle length of COPA had be increased from 21 to 28 days when this regimen was administered concurrently with interferon, due to the increased myelotoxicity of the combination. The most commonly used anthracycline-containing regimen in the U.S. for treatment of NHL, 21-day cycles of CHOP for 6-8 cycles, has been reported to have significant incidence of grade 3 and 4 myelosuppression (47% neutropenia, 7% anemia, and 6% thrombocytopenia). In order to deliver a tolerable treatment, the current CHOP regimen would require modification (alteration of the drug doses and/or cycle length) if given in conjunction with interferon. However, it is unlikely that even with dose adjustments, treatment with combination chemotherapy for up to 18 months is likely to be utilized in the U.S. It remains unclear as to whether the results of the GELF study would be replicated in a population in whom a shorter duration of interferon was utilized. Given that many of the supportive studies from the literature utilized maintenance therapy and the fact that the GELF study used a form of maintenance interferon with attenuated chemotherapy, there is no way to address the relative importance of the duration of interferon use to the overall effect of prolonging progression-free survival. Only one study, the ECOG trial, was conducted to evaluate the role of chemoimmunotherapy for initial treatment without maintenance. Patients in this study received 8-10 months of treatment, which is prolonged compared a standard CHOP regimen

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X. Appendices

Appendix A: Abbreviations used in text

AE	Adverse event.
BLA	Biologics licensing application.
CEOP	Cyclophosphamide, epirubicin, vincristine (Oncovin), prednisone.
Chlb	Chlorambucil.
CHOP	Cyclophosphamide, doxorubicin, vincristine (Oncovin), prednisone.
CHVP	Cyclophosphamide, doxorubicin, teniposide (VM-26), prednisone.
COP	Cyclophosphamide, vincristine (Oncovin), prednisone.
COPA	Cyclophosphamide, vincristine (Oncovin), prednisone, doxorubicin (Adriamicin).
CR	Complete response.
CRF	Case report form.
CYCLOPHOSPHAMIDE	Cyclophosphamide.
CVP	Cyclophosphamide, vincristine, prednisone.
DI	Dose intensity.
DPDL	Diffuse poorly differentiated lymphocytic.
DWDL	Diffuse well differentiated lymphocytic.
ECOG	Eastern Cooperative Oncology Group.
EORTC	European Organization for Research and Treatment of Cancer.
FL	Follicular lymphoma.
FM	Follicular Mixed.
GELA	Groupe d'Etude des Lymphomes de l'Adult.
GELF	Groupe d'Etude des Lymphomes Folliculaires.
HGF	Hematopoietic growth factor.
IFN	Interferon.
ITT	Intent to treat.
IU	International units.
IWF	International Working Formulation
KS	Kaposi's sarcoma.
MIU	Million international units.
MR	Minor regression.
MTX	Methotrexate.
NH	Nodular histiocytic.
NHL	Non Hodgkin lymphoma.
NPDL	Nodular poorly differentiated lymphocytic.
ORR	Overall response rate.
OS	Overall survival.
PD	Progression, progressive disease.
PFS	Progression-free survival.

PLA ..... Product licensing application.
PmM ..... Prednimustine & Mitoxantrone.
PR ..... Partial response.
SD ..... Stabilization, stable disease.
TIW ..... (three times per week)
UTI ..... Urinary tract infections.
VM-26 ..... Teniposide.